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Systematic study on acylation of methyl 3-aminocrotonate with acid chlorides of aliphatic, aromatic and α, β-unsaturated acids: A comparative evaluation of the preference for regio- and stereoselectivity *vis-à-vis* 3-aminocrotononitrile

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Acylation of methyl 3-aminocrotonate **1a** in benzene with a variety of aliphatic and aromatic acid chlorides including α, β-unsaturated acid chloride in the presence of an added organic base, (either pyridine or triethylamine) is reported. The preferred N, C-site selectivity in these reactions has been compared with the terminal selectivity of the products obtained previously on acylation of methyl 3-aminocrotononitrile **1b**. A strong preference either for N- or C- selectivity in N, C-acylation has been observed for both **1a** and **1b** based on the choice of acid chlorides and added organic base. Interestingly, irrespective of the enamine **1a** or **1b**, acylation with α, β-unsaturated acid chlorides in the presence of triethylamine afforded 3,4-dihydropyridin-(2*H*)-one *via* [3.3] sigmatropic rearrangement of the corresponding intermediary N(E)-enamide. Accrued results show methyl 3-aminocrotonate to be a better precursor for preparation of enamides (N-acylated products) whereas 3-aminocrotononitrile is found to be a preferred choice for preparation of enaminones (C-acylated products). An attempt is made to offer a preliminary theoretical interpretation for observed site selectivity.

Keywords: Methyl 3-aminocrotonate, acylation, enaminones, enamides, regioselective, stereoselective

Enamines represent a three atom π-system, and in principle, can react with an electrophile either on nitrogen or on carbon leading to the formation of enamides (N-acylated) or enaminones[1] (C-acylated). Chemistry of enamines are reported extensively but these are mostly related to tertiary cyclic enamines. In sharp contrast, significantly much less work were reported on the chemistry of acyclic primary enaminonitriles and enaminoesters[2]. Enaminoesters are versatile, readily available highly important synthetic intermediates and building blocks in organic chemistry[3] particularly in the synthesis of heterocyclic compounds[4] and alkaloids[5]. In addition, enaminones also serve as important precursors for synthesis of valuable therapeutic and biologically active molecules *e.g.* anticonvulsirant[6], antitumor[7]. Moreover, enaminones also find use as useful intermediates for the preparation of aminoester[8] including α, β-unsaturated aminoesters, peptides[9] antimicrobial andantitumors[10]. Preparation of enaminones from benztriazole are well documented[11]. Most commonly used methods for preparation of enaminones involve catalytic amination of 1,3-diketones. Conventional catalysts employed are ceric ammonium nitrate (CAN)[12], $ZrOCl_2$[13], gold(I)/silver(I)[14], $Pd(PPh_3)_2Cl_2$[15], Indium TosMIC[16]. Preparation of enaminones *via* rhuthenium catalysed coupling of thioamides and α-diazocarbonyl compounds is also reported[17]. A rich source of enaminones results either through base induced cleavage[18] or reductive ring cleavage[19] of suitably substituted isoxazoles along with samarium diiodide assisted[20] isoxazole ring opening. Benzotriazole and 2,2,4-trimethyl-2-oxazoline have found applications as strong acylating agents for metalated ketimine acylation leading to the formation of enaminones in high yield[21]. Catalytic amination of 1,3- diketones producing N-substituted enaminones, however, has some serious limitations for large scale preparations in terms of. high reaction time, temperature, catalyst cost and loading. Regio and chemoselective preparation of enaminones could only be achieved with symmetrical 1,3-diketones[22] or 1,3-dicarbonyl compounds having substantially different carbonyl reactivity[23].

Enamides, like enaminones, are stable enamine surrogates and provide key intermediates for the synthesis of small but complex nitrogen containing heterocycles and display a fine balance of stability

and reactivity leading to their increasing multiple uses in organic reactions and synthesis[24]. Preparation of enamides generally involves reductive acylation of oximes and ketoximes[25]. Substituted 3-aminoquinolines were synthesised from ethyl N-pivaloyl-3-aminocrotonate[26].

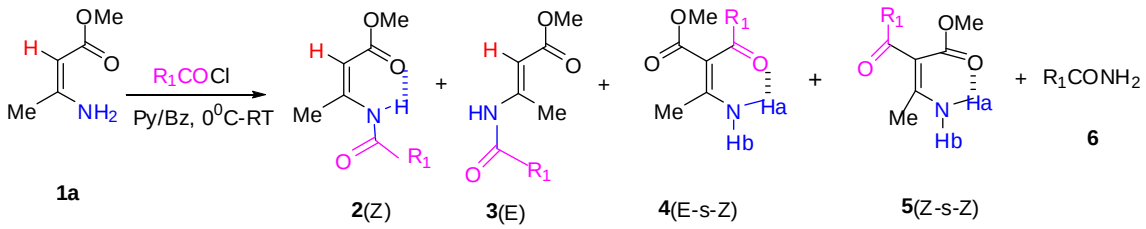
Since enamines display pronounced ambident properties in C=C-N atom triad, one could envisage a very simple synthetic protocol for preparation of enaminones or enamides from a common precursor by reacting enamines with acid chlorides provided N,C site selectivity in the triad is ensured. In the past, following this strategy we successfully developed[27] a highly regioselective preparation of enaminones and enamides in excellent yields by reacting 3-aminocrotonitrile **1b** with acid chlorides. Initially, the reaction was carried without an added organic base when polymerization of **1b** was found to occur while use of triethylamine resulted in the formation of acid anhydride. Use of pyridine as an added organic base offered the best results. Saturated acid chlorides when reacted with **1b**, complete regioselectivity either at C-terminal or at N-terminal, was observed[27]. Interestingly, reaction with aliphatic or aromatic α,β–unsaturated acid chlorides produced 3,4-dihydropyridin-(2*H*)-ones *via in situ* [3,3] sigmatropic rearrangement of the incipient enamides[28]. In contrast, during acylation of **1b** with aromatic acid chlorides no such clear cut regioselectivity could be observed. Steric and electronic influence of an aromatic nucleus on the regio or stereochemical outcome in acylation of enamines is well recognized. Preference for terminal selectivity appears to be largely dependent on (i) choice of aliphatic/aromatic acid chlorides, (ii) position and nature of the substituents (EDG/EWG) and (iii) nature of added organic base.

Easy excess to α-enaminones in high yields allowed us to develop, for the first time, a regiospecific general synthesis of contiguously substituted 1,2–azoles *i.e.* pyrazoles[29], isoxazoles[30] and isothiazoles[31] from a common precursor.

EWG variants present in the examine moiety is known to exert strong influence in terminal site selection during acylation[32]. Encouraged by earlier success in ensuring regioselectivity in N,C-acylation of 3-aminocrotononitrile **1b**, the present investigation was undertaken with methyl 3-aminocrotonate (**1a)** in order to ascertain (a) relative efficacy of this system pertaining to useful synthetic applications and (b) to compare the derived results *vis-à-vis* with **1b.** Accrued information is expected to provide an insight to the preferred regio and stereoselectivity in N,C-acylation of these enamines *e.g.* **1a** and **1b** (Scheme I). To the best of our knowledge, till now, no such comparative study on the regio- and stereoselectivity in N,C-acylation of enaminoesters **1a** and enaminonitrile **1b** is reported or compiled. The present work reports the results of this investigation.

Results and Discussions

Early researchers reported[2b,c,d,h,33] some preliminary work on acylation of more commonly used ethyl 3-aminocrotonate. However, lack of any systematic investigation on the regioselectivity in N,C-acylation of methyl 3-aminocrotonate (**1a**) prompted us to undertake this work. In the present study, acid chlorides used for acylation of **1a** were classified under the following heads: (i) aliphatic straight and branched-chain aliphatic acid chlorides (ii) acid chlorides of substituted acetic acid (iii) aromatic acid chlorides with or without substituent(s) and (iv) α,β-unsaturated acid chloride. Assignment of structure for the derived acylated products of **1a** are expected to be quite complex. Theoretically, four stereoisomers could result and in some cases formation of amide was also reported (Scheme I). In view of regio- and stereochemical complexity associated with the structure of the reaction products, successful



R_1= a) CH_3, b) CH_2CH_3, c) $CH(CH_3)_2$, d)$CHCl_2$ e) $CH_2OC_6H_5$, f) $CH_2OC_6H_3Cl_2(2,4)$, g) Ph, h) $C_6H_4Cl(o)$, i) $C_6H_4Cl(m)$, j) $C_6H_4Cl(p)$, k) = $C_6H_5CH=CH$

Scheme I

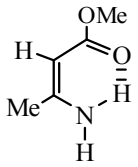
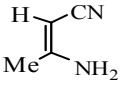
application of this strategy in synthesis rests entirely on unambiguous structural assignment. Thankfully, acylated regio- and stereoisomers can easily be differentiated, identified and unequivocal assignment of the structure of the regio/srereoisomers could be achieved from extensive NMR spectral. analysis (Experimental). Presence of C- and N-acylated products in the reaction mixture is characterised by appearance of three broad signals due to the presence of two sets of NH protons. The chelated NH signal for the N(Z)-isomer, secured by an intramolecular hydrogen bond between NH and C=O group, appears at a very low field (δ 11-13 ppm) whereas for the C(E)-isomer, the –NH proton signal appears at δ 7.5-8.5ppm. The ratio of the regio/stereoisomers present in the reaction mixture can also be easily determined from the integration values of C-Me signals for C- and N- acylatyed products. For the chelated Z-isomer, the shift for methyl protons is about 0.1 ppm down field and the vinylic hydrogen is about 1.9 ppm upfield as compared to the E-isomer. Shift differences are also observed in ^{13}C NMR spectra[33] especially signals for those of C-2, C-3 and C-4.

(a)Acylation of methyl 3-aminocrotonate 1a with straight and branched-chain aliphatic acid chlorides

In our study acylation was conducted by addition of acid chlorides of acetic acid and propionic acid into methyl 3-aminocrotonate (**1a)** in benzene in the presence of pyridine at 0°C and the reaction mixture was allowed to attain room temparature when only (Z)-enamides **2a** and **2b** were obtained in excellent yields (Scheme I, Table I). Enamide **2a** was also prepared[34] from **1a** by reacting with refluxing acetic anhydride.

Interestingly, reaction of these acid chlorides with **1b** showed complete reversal of site selectivity producing only C-acylated compounds[27a].When acylation of **1a** was extended to branched–chain aliphatic acid chloride namely acid chloride of isobutyric acid, a colorless liquid was obtained. (TLC and GC showed the presence of two compounds

Table I — N,C- acylation of **1a** and **1b**with aliphatic and aromatic acid chlorides (R_1COCl): Comparison of preference for regio- and stereoisomers

Entry No.	R_1COCl	 **1a**	Yield (%)	 **1b**	Yield (%) Lit[27]
		Product (N,C)		Product (N,C)[27]	
1	a) R_1= CH_3	**2a** (N, *Z*)[34]	72%	(C, Z)	70%
2	b) R_1= CH_2CH_3	**2b**(N, *Z*)	70%	(C, Z)	77%
3	c) R_1= $CH(CH_3)_2$	**2c** (N, *Z*)	75%	(N, E)	78%
4	d) R_1= $CHCl_2$	**4d**(C, *E*-*s*-*Z*)	80%	(C, *Z*)	71%
5	e) R_1= $CH_2OC_6H_5$	**2e**(N, *Z*)	42%	(C, Z)	85%
		4e (C, *E*-*s*-*Z*)	35%		
		5e(C, *Z*-*s*-*Z*)	14%		
6	f) R_1= $CH_2OC_6H_3Cl_2$(2,4)	**2f** (N, *Z*)	40%	(C, *Z*)	85%
		4f(C, *E*-*s*-*Z*)	32%		
		5f(C, *Z*-*s*-*Z*)	20%		
7	g) R_1= Ph	**2g** (N, *Z*)	50%	(C,Z& N, E)	80%
		6g	20%		
8	h) R_1= C_6H_4Cl (*o*)	**2h** (N, *Z*)	70%	(N, E)	71%
9	i) R_1= C_6H_4Cl (*m*)	**2i** (N, *Z*)	69%		70%
		4i & 5i	10%	(N, E)	
		(C, E &C,*Z*)			
10	j) R_1= C_6H_4Cl (*p*)	**2j**(N, *Z*)	60%		74%
		4j& 5j	15%	N,E& C, Z	
		(C, *E* & C, *Z*)			

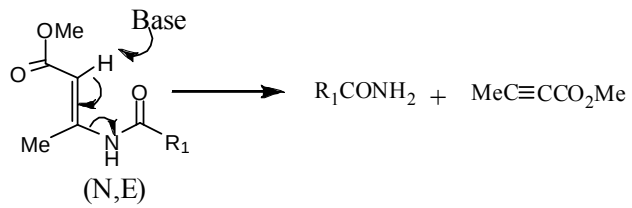
(R_t = 3.165 min; 82%) and (R_t =3.255 min; 17%). Column chromatography (4% ethyl acetate – pet.ether) afforded the Z- isomer of the N-acylated product **2c** along with a small amount of amide **6c** resulting from **3c.** The suggested mechanism is depicted in Scheme II. This exclusive preference for N-terminal selectivity was in agreement with the result obtained previously when 3-aminocrotononitrile **1b** was reacted with isobutyryl chloride[27] (Table I, Scheme II).

(b) Acylation of methyl 3-aminocrotonate 1a with substituted acetyl chlorides

In order to get further insight into site selection priority in N,C-acylation, substituted acetyl chlorides, in the presence of pyridine, were reacted with **1a**. Dichloroacetyl chloride afforded exclusively the C-acylated **(**E-s-Z) compound **4d** in high yield (80%) (Table I). It was reported[34] that reaction of amines with dichloroacetyl chloride in the presence of triethylamine prefers N-acylation producing dichloroacetamido *via* dichloroketene Cl_2=C=O which reacted with the more nucleophilic nitrogen centre[35]. This observation once more highlights the imperative importance of the nature of the added organic base in N,C-site selectivity.

Phenoxyacetyl chloride and 2,4-dichlorophenoxyacetyl chloride, on the other hand, provided a complex mixture of C-and N-acylated products as revealed from examination of ^{1}H NMR spectrum of the crude reaction mixture. Pure compounds were isolated by column chromatography and were subjected to exhaustive spectral analyses. Both phenoxyacetyl chloride and 2,4-dichlorophenoxyacetyl chloride were found to produce N-acylated product and a pair of stereoisomeric C-acylated compounds. Thus, for phenoxyacetyl chloride, these were **2e** (N,Z; 42%), **4e (**C,E-s-Z;14%) and **5e** (C,Z-s-Z;35%) whereas 2,4-dichlorophenoxyacetyl chloride produced **2f** (N,Z; 40%), **4f** (C, E-s-Z; 20%) and **5f** (C, Z-s-Z; 32%). (Table I). Gross structure of **4f** and **5f** could easily be ascertained from their mass spectra (317.1M$^+$) and elemental analyses. However, fine structure of the C-acylated products could only be established through extensive analysis of the NMR spectra including 2D-NMR(ROE) experiments, results of which correlate nicely with the assigned configuration.

The structure of E-s-Z and Z-s-Z isomer of C-acylated product was unequivocally proved by 2D-NMR (ROE). Further, Z-isomer can easily be differentiated from E-isomer as its chelated NH proton signal appears at a much low field (δ 10.48-10.68 ppm) compared to NH proton signal for E-isomer appearing at δ 9.77-9.87 ppm.



Scheme II

(c) Acylation of methyl 3-aminocrotonate (1a) with aromatic acid chlorides

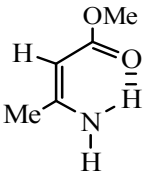
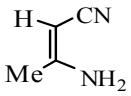
Acylation of **1a** was further extended to aromatic acid chlorides (Table I). Thus, benzoyl chloride on reacting with **1a** in the presence of pyridine afforded, after column chromatography, two products. Spectral analysis showed the major product being (Z)-enamide **2g** and the minor one was found to be benzamide **6g** resulting from **3g** (Scheme II). Acylation of **1a** when carried with isomeric chlorobenzoyl chlorides gave interesting results. *o*-Chlorobenzoyl chloride showed unique preference for N-terminal selection producing only the Z-enamide **2h,** while reaction with acid chlorides of *m*- and *p*-chlorobenzoic acid gave a mixture of regio- and stereoisomers namely **2i** (N,Z), **4i**(C, E-s-Z), and **5i** (C, Z-s-Z) and **2j** (N, Z), **4j** (C,E-s-Z) and **5j** (C, Z-s-Z) respectively of which Z-isomers predominate (Table II). The pair of C-acylated products were found to be present as an inseparable mixture (1:1) of stereoisomers as ascertained from ^{1}H- NMR spectral analyses.

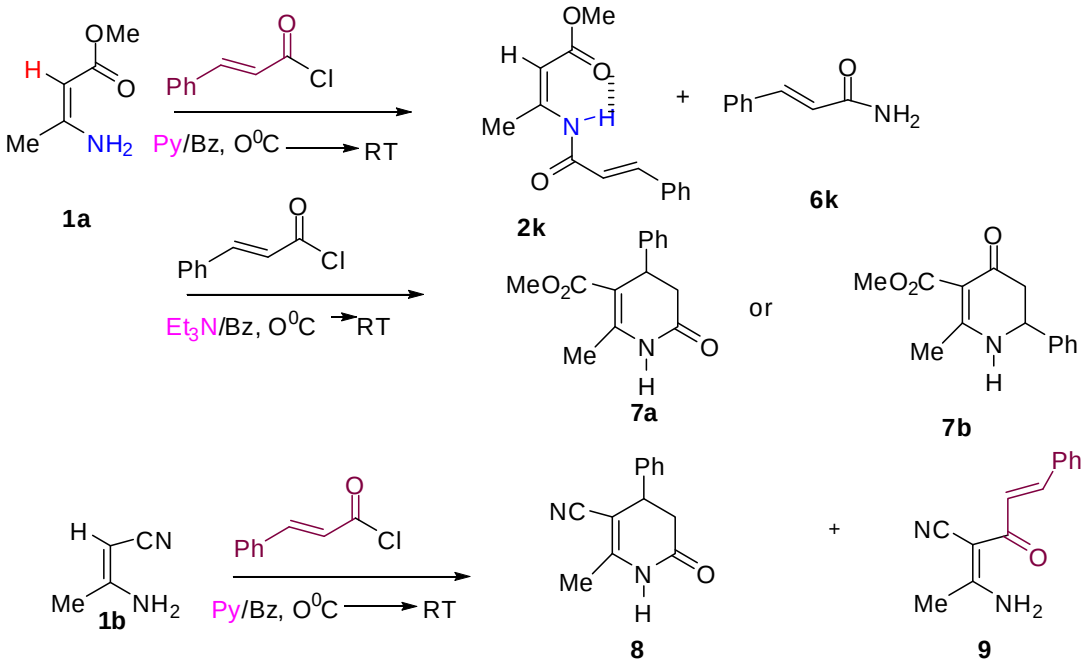
(d) Acylation of 1a with α, β- unsaturated acid chlorides (cinnamoyl chloride)

Our earlier work[28] showed that enaminonitrile **1b** when reacted with α,β- unsaturated aliphatic or aromatic acid chlorides in the presence of triethylamine afforded pure 3,4-dihydropyridin-2(1H)-one **8** as the only product in high yield**.** It is pertinent to mention that Benary[2] reported formation of a mixture (1:1) of C-and N-acylated compounds when **1b** was reacted with cinnamoyl chloride in the presence of pyridine. We reinvestigated[36] this reaction under Benary condition and isolated compounds **8** and C(Z)-acylated enaminonitrile **9** but could not detect (^{1}H NMR) any trace of N-acylated isomer in the reaction mixture. Benary designated N-acylated product was thus found to be dihydropyridone **8** and not the free enamide.

In order to ascertain if there be any difference in preferential C,N-site selectivity in acylation of enaminoester *vis-à-vis* enaminonitrile, methyl 3-aminocrotonate **1a** was initially reacted with cinnamoyl chloride in the presence of pyridine, the reaction mixture showed presence of two compounds (TLC; 1:4 ethyl acetate – petether). ^{1}H NMR spectral analysis of the pure materials (column chromatography) showed these to be the N(Z)-acylated compound **2k** and cinnamamide **6k** (Scheme II). Product composition of this reaction is quite revealing when compared with the reaction products obtained earlier with **1b.** Formation of **2k** along with **6k,** clearly a hydrolysed by-product of **3k,** demonstrates exclusive preference for N-acylation in **1a**. Complete absence of dihydropyridone in the reaction mixture suggests that only E-enamide and not Z-enamide participates in its formation. This conclusion was further supported by the fact that Z-enamide even failed to induce cyclization in refluxing diphenyl ether. However, when pyridine was replaced by triethylamine as an added organic base, a highly crystalline material in high yield was obtained as the sole product. Spectral analyses (UV, IR, ^{1}H NMR, MS) indicated gross structure of this compound to be either 3,4-dihydropyridin-2(1H)-one **7a** or 3,4-dihydropyridin-4(1H)-one **7b** (Scheme III). Since these two systems are vinylogous. UV, IR and ^{1}H NMR data could not be used for unambiguous structural assignment[37].

Table II — Acylation of **1a** and**1b** with unsaturated acid chloride in presence of pyridine and triethylamine

Base	 **1a**	Yield (%)	m.p. (°C)	 **1b**	Yield (%)[28]	m.p. (°C)[28]
	Product			Product[28]		
Pyridine	**2k**	30	70-72	**8**	38%,	196-197
Et_3N	**6k**	60	148-150	**9**	62%	189
	7a	75	180-182	**8**	80%	189



Scheme III

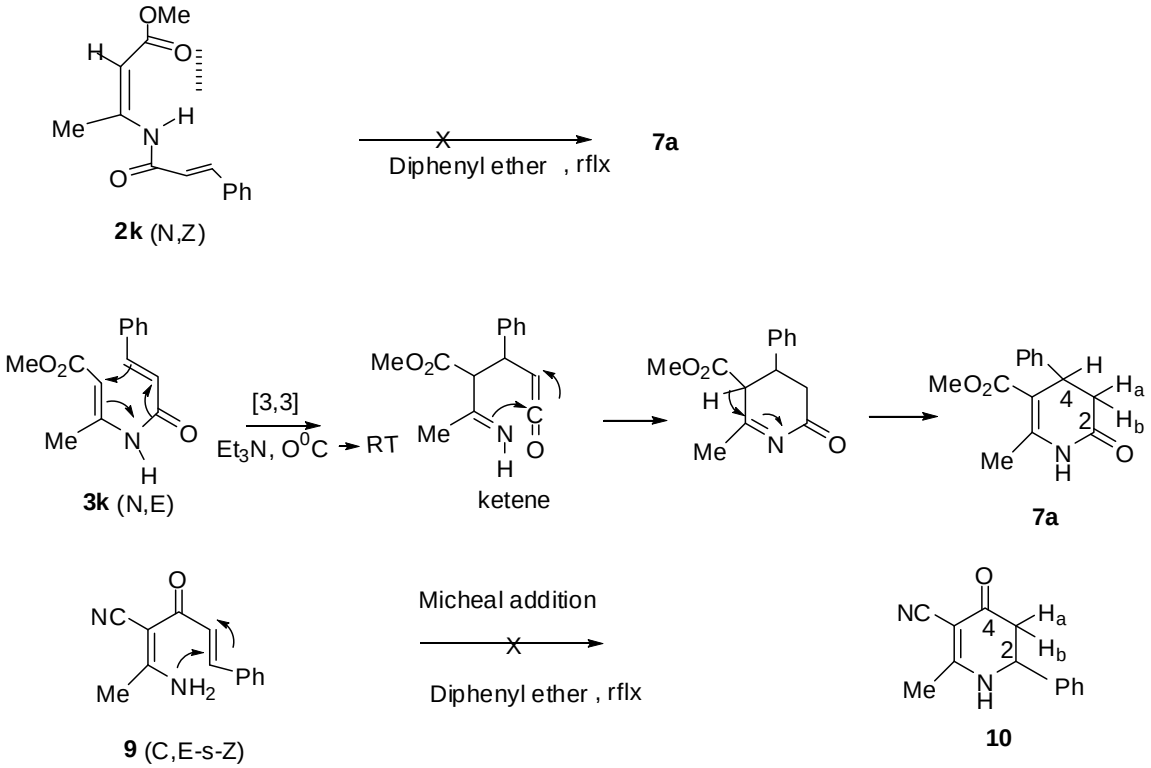
Mechanistically, **7a** could result *via in situ* [3.3] sigmatropic rearrangement of the intermediary N(E)-acylated isomer **3k.** However**,** as observed[36] previously with **1b**, C-acylated enaminonitrile **9** failed to undergo intramolecular Michael addition in refluxing diphenyl ether to produce 3,4-dihydropyridin-4(1H)-one **10** (Scheme IV). Thus, it was quite apparent that 3,4-dihydropyridin-2(1H)one **7a**and not 3,4-dihydropyridin-4(1H)-one **7b** was formed in this reaction (Scheme IV). This conclusion was further supported[38,39] by ^{13}C NMR spectral analysis of compound **7a** wherein signals appearing at δ 171.27 (amide C=O), 167.72 (ester C=O) and 38.08 (C-4) ppm unequivocally supports the fine structure in favour of **7a**.

Plausible explanation for regioselectivity in C, N-acylation

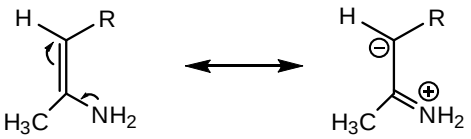
Regioselectivity in C, N-acylation of enamines depends largely among others on the choice of the reacting acid chlorides and the added organic base. According to principle of least nuclear motion (PLNM) concept[40] less reorganisation is needed for attack at N-site of the enamines. This preference for N-terminal is also supported from 'Hoz effect'[41] which predicts lower intrinsic barriers for attack at the atom further right in the periodic table. In view of these observations, one may qualitatively assume that N-attack is intrinsically preferred *i.e*. acylation of enamines is expected to give N-acylated products.

Examination of the results obtained with **1a** and **1b** reveals some striking features with regard to preference for regio and stereoselectivity in N,C-acylation. Acyl chlorides, the added organic base and reaction conditions remaining same, it was found that substituent variants R in enamines tend to show distinct preference for site selection. Such unique site preference in N,C-acylation in these systems may be explained from the stability of their zwitterionic structure.

Between -CN and -CO_2Me groups, -CN has more pronounced electron withdrawing effect than -CO_2Me and because of this, zwitterionic form is more stabilized in case of **1b** (Figure 1). Acylation thus occurs, in most of the cases studied, preferentially at C-nucleophilic centre rather than nucleophilic free N centre of **1b** (Exception with isobutyryl chloride (exclusively N- acylation), benzoyl and isomeric



Scheme IV



1a R= -CO_2Me, **1b** R= -CN,

Figure 1

chlorobenzoyl chloride (mixture of C&N)) whereas preferential N-acylation occurs in case of **1a** (except dichloroacetyl chloride (exclusively C-acylation) and phenoxy and dichlorophenoxyacetyl chloride (1:1 N & C), isomeric chlorobenzoic acid (10-15% C-acylation)).

Conclusion

The present study highlights the importance of the choice of the enamines as regio- and stereoselectivity in N,C-acylation is found to be largely dependent on their properties.

This study further demonstrates that site selection in N,C-acylation, among other factors, is significantly dependent on the character of the added organic base. In our investigation we found that use of pyridine offered the best results. Use of triethylamine as an added organic base resulted in poor yields of the acylated products either due to polymerisation of the enamine or formation of the acid anhydride. Contrary to this observation, reaction of α,β-unsaturated acid chlorides with enamines **1a** and **1b** in the presence of triethylamine as an added organic base produced the best results in terms of regioselectivity and yields, providing an excellent route for regiospecific preparation of contiguously substituted 3,4-dihydropyridin-2(1H)-ones in a clean and high yielding reaction.

N(Z)-enamide **2k** under refluxing diphenyl ether failed to cyclize to form **7a**. Mechanistically this observation is extremely significant. Failure of N(Z)-stereoisomer to undergo cyclization clearly demonstrates that only N(E)- stereoisomer participates in (3,3)-sigmatropic rearrangement leading to formation of **7a.** Triethylamine, being a stronger amine probably pushes the equilibrium towards transient E-enamide.

A close examination of ^{1}H NMRspectral data of the acylated products obtained from **1a** revealed that N-acylated products exists in *Z*-configuration only. The C-acylated products, on the other hand, were found to be present as a mixture of stereoisomers (*Z*, *E*), but with a clear preference for *E*-isomer. Comparison of the results obtained in N, C- acylation with **1a** and **1b** clearly demonstrates that choice of enaminonitrile **1b** rather than enaminoester **1a** would be more attractive as far as preparation of enaminones are concerned (Table I and Table II). This unique C-selectivity of 1b is confined to aliphatic acid chlorides only. No such clear cut C-terminal preference was observed with aromatic acid chlorides. In view of simplicity of reaction, regioselective acylated products and high yields in N,C-acylation, enaminoester **1a** and enaminonitrile **1b** score over other primary enamines. Since ester and nitrile groups are chemically interconvertable use of **1b** eliminates the need for chromatographic separation of regio and stereoisomers formed in acylation with enaminoester **1a.**

N-and C-acylated enaminoesters and enaminonitriles have found extensive applications in synthesis, biological and pharmaceutical study. In view of the simplicity and high yields in N,C-acylation, methyl 3-aminocrotonate**1a** and 3-aminocrotononitrile **1b** score over other enamines in terms of preparation of regio- and stereoisomers.

In conclusion, this study for the first time, explored the comparative N,C- terminal preference of methyl 3-aminocrotonate (**1a**) and 3-aminocrotononitrile (**1b**). Since ester and nitrile groups are chemically interconvertible to many other useful functional groups, **1a** and **1b** bear complimentary relationship.

Experimental Section

Materials and Methods

Yields are given on the chromatographically pure compounds. Boiling points (bp) or melting points (mp) are uncorrected and measured in open capillary method. Solvents and reagents were purchased from Sigma-Aldrich and were purified by conventional literature methods. Thin-Layer Chromatography (TLC) was carried on precoatedGF_{254} TLC plates, flash chromatography (FC) was carried on silica gel (60-120 mesh). Gas chromatography (GC) was carried out by injecting samples in dichloromethane (DCM) through HP-1 and GC port INNOWAX capillary column, FID detector N_2 as carrier gas and maintaining the oven temperature at 40°C and then programmed to 220°C at 15°C/min in Agilnet 6890N instrument, IR spectra were recorded either neat or in KBr matrix on Hitachi 270-30 and Perkin Elmer, model spectrum-1 spectrometers. Ultraviolet spectra

in ethanol unless specified otherwise were recorded on Hitachi U-2000. NMR spectra in $CDCl_3$ or DMSO-d_6 were run on Bruker AC-200, Bruker DPX-400, Bruker Avance 400, Spect-400 and drx 500 MHz instruments. Tetramethylsilane (TMS) was used as an internal standard, δ values are reported in ppm, J values in Hertz. ^{13}C NMR assignments are derived from heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) experimemts. Mass spectra (*m/z*; rel%) were determined in Hitachi RMU 6L, JEOL JMS 600, Thermo Finnigan LCQ DUO spectrometers. Elemental Analyses were performed in Perkin-Elmer 240C elemental analyser.

General procedure for the preparation of (*Z*)-methyl (3-alkylamido)-but-2-enoates, (*Z*)-methyl (3-arylamido)-but-2-enoates and (*Z*)-and (*E*)-methyl 3-amino-2-acyl but-2-enoates and (*Z*)-and (*E*)- methyl 3-amino-2-aroyl but-2-enoates

To a magnetically stirred solution of methyl 3-aminocrotonate (1.15g, 0.01m), pyridine (0.03m) in dry benzene (15 mL) was added drop wise, freshly distilled acid chloride (0.01m) in dry benzene (10 mL) under ice-cold water. The reaction mixture was poured on to ice water on attaining ambient temperature. The mixture was extracted with ethyl acetate (3×25 mL). The organic layer was sequentially washed with cold (2N) hydrochloric acid solution (2×15 mL) to remove excess pyridine, saturated sodium bicarbonate solution until neutral and finally with brine. The organic layer was then dried over anhydrous sodium sulphate. Removal of the solvent afforded solid materials which on crystallization from a suitable solvent furnished pure acylated product **2a-2c, 2e-2j** and **4d-4f, 4i, 4j** and **5e, 5f, 5i** and **5j**.

Preparation of (*Z*)-methyl 3-acetamido-but-2-enoate, 2a: White needle-shaped crystals. Yield 72%. m.p.36°C. IR (KBr): 3584, 2470, 2306, 1719, 1618, 1552, 1436, 1255. UV (EtOH), λ_{max} in nm (ε): 340 (1401), 267 cm^{-1} (7217); ^{1}H NMR (DMSO-d_6): δ 2.10 (3H, s, C*H*$_3$), 2.30 (3H, s, C=CH$_3$), 3.70 (3H, s, OC*H*$_3$), 5.05 (1H, s, C=C*H*), 10.90 (1H, br, N*H*); ^{13}C NMR (DMSO-d_6): δ 21.33 (C-4), 24.83 (CO*C*H$_3$), 50.84 (O*C*H$_3$), 95.36 (C-2), 154.65 (C-3), 168.53 (C=O), 168.55 (NH*C*O); MS: *m/z* (%) 157 (26) [M$^+$], 115 (51), 84 (100), 57 (23). Anal. Found: C, 53.78; H, 7.09; N, 8.79. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.05; N, 8.91%.

Preparation of (*Z*)-methyl 3-(propionamido)-but-2-enoate, 2b: Sugar-cube shaped crystals. Yield 70%. m.p. 48°C. IR (KBr): 3516, 2990, 2916, 2460, 2306, 1719, 1617, 1438, 1391, 1336, 1262 cm^{-1}; UV(EtOH), λ_{max} in nm (ε): 338 (2619), 271 (10, 710); ^{1}H NMR ($CDCl_3$/TMS): δ 1.20 (3H, t, CH$_2$C*H*$_3$), 2.37 (3H, s, C=C*H*$_3$; 2H, q, C*H*$_2$CH$_3$), 3.70 (3H, s, OC*H*$_3$), 4.90 (1H, s, C=C*H*), 11.12 (1H, br, N*H*); ^{13}C NMR ($CDCl_3$/TMS): δ 9.04 (CH$_2$*C*H$_3$), 21.91 (C-4), 31.16 (*C*H$_2$CH$_3$), 50.86 (O*C*H$_3$), 95.67 (C-2), 155.23 (C-3), 169.45 (C=O), 172.59 (NH*C*O); MS: *m/z* (%) 171 [M$^+$] (32.5), 115 (75), 84 (100), 57 (90). Anal. Found: C, 56.38; H, 7.62; N, 8.23. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18%.

Preparation of (*Z*)-methyl 3-(isobutyramido)-but-2-enoate, 2c: Colourless liquid. Yield 75%. b.p.65-66°C /0.6mm Hg; IR (KBr): 3254, 2964, 1711, 1624, 1477, 1440, 1384, 1252 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 339 (2524), 268 (10531); ^{1}H NMR ($CDCl_3$/TMS): δ 1.22 & 1.24 (2×3H, d, *J* = 6Hz, 2×C*H*$_3$), 2.39 (3H, s, C=C*H*$_3$), 2.53 (1H, m, C*H*(CH$_3$)$_2$), 3.70 (3H, s, OC*H*$_3$), 4.92 (1H, s, C=C*H*), 11.19 (1H, br, N*H*); ^{13}C NMR ($CDCl_3$/TMS): δ 19.18 (CH(*C*H$_3$)$_2$), 21.99 (C-4), 37.10 (*C*H), 50.93 (O*C*H$_3$), 95.89 (C-2), 155.48 (C-3), 169.54 (*C*O), 175.97 (NH*C*O). Anal. Found: C, 58.61; H, 8.13; N, 7.61. Calcd for $C_9H_{15}NO_3$: C, 58.37; H, 8.16; N, 7.56%.

Preparation of (*E*)-methyl 3-amino-2-(2,2-dichloroacetyl)but-2-enoate, 4d: White crystals. Yield 80%. m.p. 64°C.IR (KBr): 3246, 3132, 1699, 1588, 1477, 1440, 1371, 1289 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 301 (15, 730), 245 (13,610). ^{1}H NMR ($CDCl_3$/TMS): δ 2.39 (3H, s, C=C*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 6.47 (1H, br, NH$_b$), 7.03 (1H, s, CHCl$_2$), 11.10 (1H, br, N*H*$_a$); ^{13}C NMR ($CDCl_3$/TMS): δ 24.66 (C-4), 51.63 (OMe), 69.61 (*C*HCl$_2$), 98.05 (C-2), 168.10 (ester C=O), 171.79 (C-3), 185.32 (keto C=O); MS: *m/z* (%) 225 (49) [M$^+$], 225.9 (35) [M$^+$+1], 228 (10) [M$^+$+3]. Anal. Found: C, 37.32; H, 4.03; N, 6.15; Calcd for $C_7H_9NCl_2O_3$: C, 37.19; H, 4.01; N, 6.19%.

Preparation of (*Z*)-methyl 3-(2-phenoxyacetamido)but-2-enoate, 2e: White needle-shaped crystals. Yield 42%. m.p. 88-89°C. IR (KBr): 3256, 1719, 1681, 1612, 1495, 1441, 1360, 1261 cm^{-1}; UV (EtOH) λ_{max} in nm (ε): 267 (15711), 216 (4561); ^{1}H NMR ($CDCl_3$/TMS): δ 2.43 (3H, s, C=C*H*$_3$), 3.72 (3H, s, OC*H*$_3$), 4.53 (2H, s, C*H*$_2$), 5.02 (1H, s, C=C*H*), 6.98-7.73 (5H, m, Ar-*H*), 12.05 (1H,

br, N*H*); MS: *m/z* (%) 257 (35) [M^+], 218 (55), 95.9 (100), 83.9 (52). Anal. Found: C, 62.42; H, 6.10; N, 5.66 Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.07; N, 5.62%.

Preparation of (*E*)-methyl 3-amino-2-(2-phenoxyacetyl)but-2-enoate, 4e: White flakes. Yield 35%. m.p 112-114°C. IR (KBr): 3272, 1678, 1598, 1448, 1433, 1286, 1220, 1123 cm^{-1}; UV (EtOH), λ_{max} in nm (ε) 263 (14987), 214 (5219); ^{1}H NMR ($CDCl_3$/TMS): δ 2.30 (3H, s, C=C*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 4.95 (2H, s, C*H*$_2$), 6.82-7.50 (5H, m, Ar-H), 8.69 (1H, br, NH_b), 10.48 (1H, br, N*H*$_a$); MS: *m/z* (%) 257 [M^+], 218.1 (52), 106.9 (100), 95.9 (93), 84 (45). Anal. Found: C, 62.39; H, 6.11; N, 5.69. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.07; N, 5.62%.

Preparation of (*Z*)-methyl 3-amino-2-(2-phenoxyacetyl)but-2-enoate, 5e: White crystals. Yield 14%. m.p.96-97°C. IR (KBr): 3422, 2944, 1690, 1599, 1564, 1548, 1487, 1433, 1343, 1223 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 289 (8221), 240 (5323); ^{1}H NMR ($CDCl_3$/TMS): δ 2.42 (3H, s, C=C*H*$_3$), 3.69 (3H, s, OC*H*$_3$), 4.52 (2H, s, C*H*$_2$), 6.58 (1H, br, NH_b), 6.84-7.37 (5H, m, Ar-*H*), 9.77 (1H, br, N*H*$_b$); MS: *m/z* (%) 257 [M^+] 218.1 (52), 106.9 (100), 95.9 (93), 84 (45). Anal. Found: C, 62.33; H, 6.09; N, 5.65. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.07; N, 5.62%.

Preparation of (*Z*)-methyl 3-(2-(2,4-dichlorophenoxy)acetamido)but-2-enoate, 2f: White flakes. Yield 40%. m.p 109-110°C. IR (KBr): 3252, 1707, 1688, 1637, 1491, 1436, 1391, 1378, 1294, 1262 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 268 (14425), 232 (8730); ^{1}H NMR ($CDCl_3$/TMS): δ 2.36 (3H, s, C=C*H*$_3$), 3.61 (3H, s, OC*H*$_3$), 4.83 (2H, s, C*H*$_2$), 5.15 (1H, s, C=CH), 7.20-7.64 (5H, m, Ar-*H*), 11.49 (1H, br, N*H*); ^{13}C NMR ($CDCl_3$/TMS): δ 21.65 (C-4, Me), 50.99 (OMe), 68.30 (*C*H$_2$), 97.51 (C-2), 122.90, 125.79, 128.14, 129.58 (Ar-C), 152.49 (C-3), 166.66 (ester keto C=O), 168.04 (amide C=O); MS: *m/z* (%) 317.1 (37.49) [M^+], 282.1 (96.44), 253 (43.33), 175 (23.55), 156.1 (100), 142.1 (64.04), 110 (83.85), 96.1 (86.58), 84.1 (16.23), 69 (21.99), 55 (15.40). Anal. Found: C, 49.28; H, 4.15; N, 4.44. Calcd for $C_{13}H_{13}NCl_2O_4$: C, 49.08; H, 4.12; N, 4.40%.

Preparation of (*E*)-methyl 2-(2-(2,4-dichlorophenoxyacetyl)-3-amino-but-2-enoate, 4f: White flakes. Yield 32%. m.p 122-124°C. IR (KBr): 3344, 2953, 1656, 1623, 1584, 1477, 1435, 1390, 1297, 1237 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 289 (12773), 236 (12004); ^{1}H NMR ($CDCl_3$/TMS): δ 2.21 (3H, s, C=C*H*$_3$), 3.65 (3H, s, OC*H*$_3$), 5.05 (2H, s, C*H*$_2$), 6.84-7.54 (5H, m, Ar-*H*), 8.79 (1H, br, NH_b), 10.68 (1H, br, N*H*$_a$); ^{13}C NMR ($CDCl_3$/TMS): δ 22.75 (C-4), 50.75 (OMe), 72.11 (*C*H$_2$), 98.22 (C-2), 114.66, 121.90, 124.00, 127.82, 129.21 (Ar-C), 153.03 (C-3), 168.31 (ester C=O), 170.58 (keto C=O); MS: *m/z* (%) 316.1 (100) [M-H]$^-$, 318.1 (65) [MH^++1]. Anal. Found: C, 49.28; H, 4.15; N, 4.44. Calcd for $C_{13}H_{13}NCl_2O_4$: C, 49.08; H, 4.12; N, 4.40%.

Preparation of (*Z*)-methyl 2-(2-(2,4-dichlorophenoxyacetyl)-3-amino-but-2-enoate, 5f: White granular crystals. Yield 20%. m.p 138-139°C. IR (KBr): 3391, 3071, 1706, 1644, 1515, 1481, 1436, 1389, 1295, 1266 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 263 (14457); ^{1}H NMR ($CDCl_3$/TMS): δ 2.32 (3H, s, C=C*H*$_3$), 3.59 (3H, s, OC*H*$_3$), 4.85 (2H, s, C*H*$_2$), 6.69 (1H, br, NH_b), 7.05-7.62 (5H, m, Ar-*H*), 9.87 (1H, br, N*H*$_a$); ^{13}C NMR ($CDCl_3$/TMS): δ 21.65 (C-4), 50.63 (OMe), 67.88 (*C*H$_2$), 99.09 (C-2), 115.12, 122.30, 125.01, 128.09, 129.50 (Ar-C), 151.46 (C-3), 167.14 (ester C=O), 167.77 (keto C=O). MS: *m/z* (%) 317.1 (18.50) [M^+], 282.1 (91.08), 258.1 (39.76), 175 (23.42), 156.1 (98.99), 142.1 (63.35), 110 (88.48), 96.1 (100), 84.1 (21.10), 68 (13.75), 55 (15.88). Anal. Found: C, 49.42; H, 4.15; N, 4.44. Calcd for $C_{13}H_{13}NCl_2O_4$: C, 49.08; H, 4.12; N, 4.40%.

Preparation of (*Z*)-methyl 3-(benzamido)but-2-enoate, 2g: White crystals. Yield 50%. m.p 45-47°C. IR (KBr): 3204, 2966, 1694, 1663, 1617, 1529, 1473, 1450, 1262 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 293 (21002), 239 (19972); ^{1}H NMR ($CDCl_3$/TMS): δ 2.40 (3H, s, C=C*H*$_3$), 3.60 (3H, s, OC*H*$_3$), 5.00 (1H, s, C=C*H*), 7.10-8.00 (5H, m, Ar-H), 11.20 (1H, br, N*H*); MS: *m/z* (%) 188 (100) [M^+-OMe], 242 (30) [M^++ Na^+]. Anal. Found: C, 66.10; H, 5.70; N, 6.45. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

Preparation of (*Z*)-methyl 3-(2-chlorobenzamido)but-2-enoate, 2h: White needle-shaped crystals. Yield 61%. m.p. 58-60°C. IR (KBr): 3250, 1709, 1670, 1630, 1430, 1263, 1183 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 340 (4098), 278 (10288); ^{1}H NMR ($CDCl_3$/TMS): δ 2.54 (3H, s, C=C*H*$_3$), 3.68 (3H, s, OC*H*$_3$), 5.05 (1H, s, C=CH), 7.34-7.60 (4H, m, Ar-*H*), 11.52 (1H, br, N*H*); ^{13}C NMR ($CDCl_3$/TMS): δ 22.11 (C-4), 51.14 (OMe), 97.63 (C-2), 127.09, 129.21, 130.66, 131.32, 131.71, 135.33 (Ar-C), 154.59

(C-3), 165.27 (ester C=O), 169.30 (amide C=O); MS: *m/z* (%) 254 (3) [MH^+], 222 (33) [M^+-OCH_3], 138.9 (100) [$C_6H_4COCl^+$], 140.9 (34) [$C_6H_4COCl^+$+2]. Anal. Found: C, 56.59; H, 4.79; N, 5.62. Calcd for $C_{12}H_{12}NClO_3$: C, 56.82; H, 4.77; N, 5.52%.

Preparation of (*Z*)-methyl 3-(3-chlorobenzamido)but-2-enoate, 2i: White crystals. Yield 69%. m.p. 75-76°C. IR (KBr): 3244, 3012, 1670, 1639, 1560, 1505, 1465, 1439, 1268, 1175 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 284 (13435); ^{1}H NMR ($CDCl_3$/TMS): δ 2.53 (3H, s, C=C*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 5.07 (1H, s, C=CH), 7.41-7.98 (4H, m, Ar-*H*), 12.11 (1H, br, N*H*); ^{13}C NMR ($CDCl_3$/TMS): δ 22.03 (C-4), 51.30 (OMe), 97.45 (C-2), 125.24, 128.28, 130.08, 132.41, 135.41 (Ar-C), 155.23 (C-3), 163.96 (ester C=O), 169.86 (amide C=O); MS: *m/z* (%) 252 (68) [M^+-1], 224 (100) [M^++2-OCH_3], 274 (37) [M^+-2+Na^+]. Anal. Found: C, 56.62; H, 4.80; N, 5.58. Calcd for $C_{12}H_{12}NClO_3$: C, 56.82; H, 4.77; N, 5.52%.

Preparation of (*E*)-methyl (2-*m*-chlorobenzoyl)-3-amino-but-2-enoate 4i & (*Z*)-methyl (2-*m*-chlorobenzoyl)-3-amino-but-2-enoate, 5i: White crystals. Yield 10%. m.p.80-85°C. IR (KBr): 3386, 3058, 1670, 1607, 1493, 1371, 1257, 1169 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 303 (11711), 211 (18226); ^{1}H NMR ($CDCl_3$/TMS): δ 2.13, 2.37 (3H, s, C=C*H*$_3$), 3.34, 3.44 (3H, s, OC*H*$_3$), 5.44 (1H, br, N*H*$_b$), 5.88 (1H, br, N*H*$_b$), 7.28-7.72 (4H, m, Ar-*H*), 9.11 (1H, br, N*H*$_a$), 10.77 (1H, br, N*H*$_a$).

Preparation of (*Z*)-methyl 3-(3-chlorobenzamido)but-2-enoate, 2j: White shinny crystals. Yield 60%. m.p 119-120°C. IR (KBr): 3216, 1618, 1480, 1465, 1439, 1265, 1171 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 290 (18302); ^{1}H NMR ($CDCl_3$/TMS): δ 2.52 (3H, s, C=C*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 5.06 (1H, s, C=C*H*), 7.46 (2H, d, *J* = 9Hz, Ar-*H*), 7.91 (2H, d, *J*= 9Hz, Ar-*H*), 12.12 (1H, br, N*H*); ^{13}C NMR ($CDCl_3$/TMS): δ 22.01 (C-4), 51.25 (OMe), 97.20 (C-2), 129.04, 129.11, 132.29, 138.80 (Ar-C), 155.44 (C-3), 164.22 (ester C=O), 169.96 (amide C=O); MS: *m/z* (%) 222 (27) [M^+-OCH_3], 224 (8) [M^++2-OCH_3], 138.9 (100) [$C_6H_4COCl^+$], 140.9 (32) [$C_6H_4COCl^+$+2]. Anal. Found: C, 56.55; H, 4.79; N, 5.60. Calcd for $C_{12}H_{12}NClO_3$: C, 56.82; H, 4.77; N, 5.52%.

Preparation of (*E*)-methyl (2,4-chlorobenzoyl))-3-amino-but-2-enoate (4j)& (*Z*)-methyl (2-(4-chlorobenzoyl))-3-amino-but-2-enoate, 5j: White crystals. Yield 15%. m.p.110-112°C. IR (KBr): 3270, 1685, 1588, 1438, 1284, 1193 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 301 (10360), 245(12738); ^{1}H NMR ($CDCl_3$/TMS): δ 2.11, 2.37 (3H, s, C=C*H*$_3$), 3.34, 3.45 (3H, s, OC*H*$_3$), 5.28 (1H, br, N*H*$_b$), 5.71 (1H, br, N*H*$_b$), 7.31-8.04 (4H, m, Ar-*H*), 9.08 (1H, br, N*H*$_a$), 10.74 (1H, br, N*H*$_a$).

Preparation of (*Z*)-methyl 3-(cinnamido)but-2-enoate, 2k: White flakes. Yield 30%. m.p. 70-72°C. IR (KBr): 3266, 3116, 2190, 1617, 1481, 1442, 1325, 1243 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 306 (19183); ^{1}H NMR ($CDCl_3$/TMS): δ 2.50 (3H, s, C=C*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 5.00 (1H, s, C=CH), 6.54 (1H, d, *J* = 15Hz, *H*C=CHPh), 7.39-7.57 (5H, m, Ar-*H*), 7.62 (1H, d, *J* = 15Hz, HC=C*H*Ph), 11.42 (1H, br, N*H*); MS: 246 (5) [MH^+], 268 (25) [M^++Na^+]. Anal. Found: C, 68.77; H, 6.19; N, 5.58. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71%.

Preparation of methyl 1,2,3,4-tetrahydo-6-methyl-2-oxo-4-phenyl pyridine-5-carboxylate, 7a: White crystals. Yield 75%. m.p. 180-182°C. IR (KBr): 3218, 3102, 1686, 1625, 1492, 1453, 1379, 1318, 1287, 1206 cm^{-1}; UV (EtOH), λ_{max} in nm (ε): 281 (15312); ^{1}H NMR ($CDCl_3$/TMS): δ 2.37 (3H, s, C=C*H*$_3$), 2.63 (1H, d, *J*=16.08 Hz, H_a), 2.85 (1H, dd, *J*= 8.06 Hz & 16.52 Hz, H_c), 3.60 (3H, s, OC*H*$_3$), 4.19 (1H, d, *J*= 7.75 Hz, H_b), 7.28 (5H, m, Ar-*H*), 8.11 (1H, br, N*H*); ^{13}C NMR ($CDCl_3$/TMS): δ 19.58 (6-Me), 38.09 (C-3), 38.44 (C-4), 51.83 (OMe), 107.37 (C-5), 127.06, 127.40, 128.97, 129.18, 129.41, 142.25 (Ar-C), 146.79 (C-6), 167,72 (C=O), 171.27 (C-2); MS: *m/z* (%) 245.1 (70) [M^+], 213 (82), 186 (100), 157 (18), 131 (20), 115 (14), 77 (12). Anal. Found: C, 68.74; H, 6.20; N, 5.76. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5%.

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